MCR-Based Exploitation and Application of Diverse (Poly)Heterocyclic Scaffolds

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SUMMARY AND FUTURE PERSPECTIVES

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The aim of this dissertation is to discuss environmentally friendly component used in multicomponent reaction chemistry, to apply MCR chemistry on scaffolds significant for medicinal chemistry applications and to implement new modalities (PROTACs) in drug design and medicinal chemistry.

In **chapter 1**, the employment of ammonia in Ugi reactions is covered, as it is inexpensive, easily available and permits reduced waste. The Ugi-type ractions is by far one of the most powerful tools leading to high structural diversity and molecular complexity. Ammonia is one of the most produced and consumed chemicals in the world. Despite the great synthetic potential of Ugi reactions and wide applications of ammonia, the utilization of ammonia in Ugi Reactions is limited by producing products in low yields or complex product mixtures are often obtained. This review details developments of solvents, reaction conditions and starting materials in ammonia-Ugi reactions, which enable the fast and efficient production of new structural frameworks comprised of a variety of biologically relevant templates. Representative examples will also be given demonstrating the successful applications of ammonia-Ugi reactions spanning peptides, heterocycles, macrocycles, and natural products syntheses respectively.

Developing more efficient techniques for synthesizing complex drug molecules is painstaking but urgent, as we are facing incredible breakthroughs in the area of identifying novel biological targets on a molecular level. Multicomponent and reactions allow scientists to carry out chemical syntheses in fewer steps than conventional approaches which can quickly generate novel chemical structures in lead discovery and optimization. The sequencing of multicomponent reactions (MCRs) and subsequent modifications is a powerful strategy for the rapid construction of diverse (poly)heterocyclic scaffolds. In **chapters 2**-**8**, applications of multicomponent reactions in a number of intriguing scaffolds are presented (Figure 1).

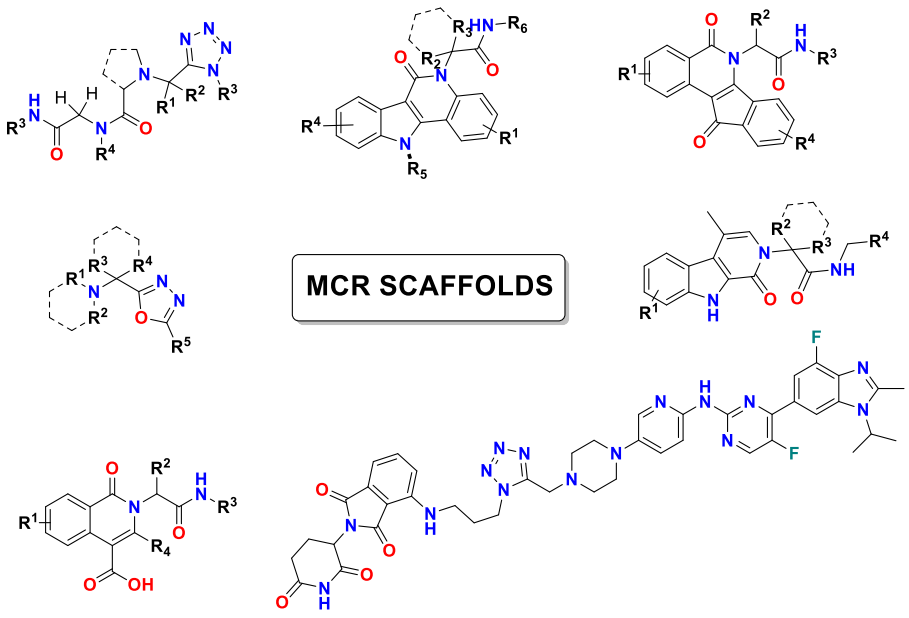

Figure 1. Scaffolds accessed via multicomponent reaction schemes.

In **chapter 2**, our aim is to directly use of C,N-unprotected amino acids in the Ugi-tetrazole reactions to produce a novel class of acid-tetrazole compounds. Surprisingly, only tetrazole Ugi product is found and not traces of other possible Ugi type reactions. Based on this reaction pathway we have designed the synthesis of novel tetrazole-peptidomimetics. A high level of structural diversity can be achieved with this isocyanide based multicomponent reactions (IMCRs), providing a platform for the production of functionalized building blocks for novel bioactive molecules and nontraditional scaffolds which previously were not accessible.

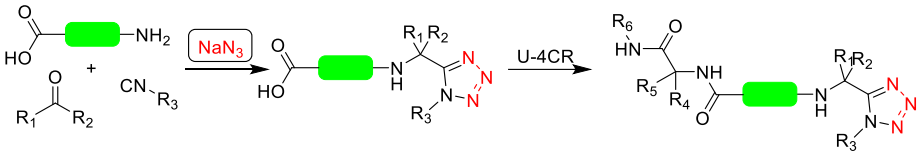

Figure 2. Concise synthesis of tetrazole-peptidomimetics by two consecutve Ugi reactions.

In **chapter 3**, we shift our focus from natural product analogues to hetercocycles. Heterocycles are used extensively in medicinal chemistry and in most of the drugs on the market, at least one heterocyclic ring is present. They are used to increase biological affinity and tune the pharmacokinetic/pharmacodynamics properties of the molecules. Therefore, there is a constant need for developing better, faster and more efficient synthetic routes for heterocyclic compounds. We demonstrate that the combination of Ugi-tetrazole and Huisgen reactions successfully leads to poly-substituted 1,3,4-oxadiazoles. It should be noted that 1,3,4-oxadiazoles are known bioisosteres for amides and esters and have various applications in medicinal chemistry and material science. With our methodology, numerous secondary amines, such as piperazine, morpholine and piperidine, that are known to be beneficial for solubility and tuning of PK/PD properties, are incorporated easily in the scaffold. A library of derivatives with high diversity was synthesized and it was shown that the method has excellent scalability and it tolerant to post-modifications.

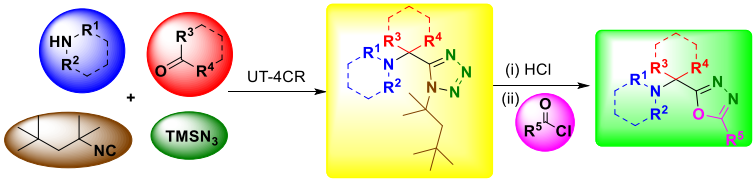

Figure 3. 1,3,4-Oxadiazoles by Ugi-tetrazole and Huisgen reaction.

The combination of multicomponent reactions (MCRs) and transition metal-catalyzed post transformations provides an enormous capability to generate molecular complexity and diversity in a minimum number of step. In **chapter 4**, we show the potential of Ugi reactions in synthesizing complex indole-fused polyheterocycles. Indole-fused scaffolds, are not only observed in natural products, but are also useful in medicinal chemistry. A variety of synthetic methods is already described, however to the best of our knowledge, MCR reactions have not been applied previously in the synthesis of this scaffold. The initial Ugi product undergoes a palladium catalyzed-reaction towards the desired indolo[3,2-*c*]quinolinones. Remarkably, diversity can be achieved through all four-components of the Ugi reaction; the aniline, the aldehyde/ketone, the isocyanide and the indole-2-carboxylic acid. Regarding potential applications, docking studies indicate that these types of derivatives could be useful as kinase inhibitors.

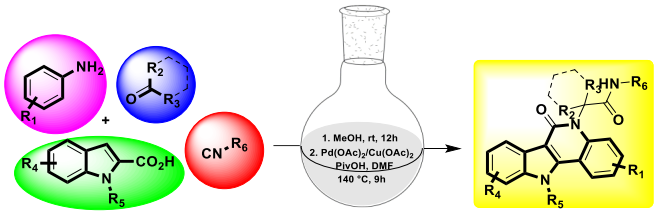

Figure 4. Pd-catalyzed de novo synthesis of indolo[3,2-*c*]quinolinones.

In **chapter 5**, easy operation, readily accessible starting materials, and short syntheses of the privileged scaffold indeno[1,2-*c*]isoquinolinone was achieved by a MCR-based protocol via an ammonia-Ugi-4CR/Copper-catalyzed annulation sequence. Optimization and scope and limitations of this short and general sequence are described. The methodology allows an efficient construction of a wide variety of indenoisoquinolinones in just two steps.

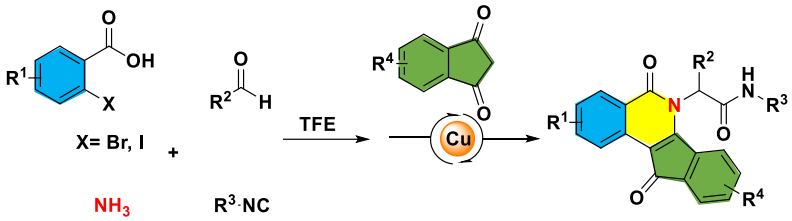

Figure 5. Copper-catalyzed modular assembly of indeno[1,2-*c*]isoquinolinones.

In **chapter 6**, a Cu-catalyzed cascade reaction were successfully applied in the Ugi postcyclization strategy by using ammonia and 2-halobenzoic acids as key building blocks. Priviledged polysubstituted isoquinolin-1(2*H*)-ones were constructed in a combinatorial format with generally moderate to good yield. The protocol, with ligand-free catalytic system, shows broad substrate scope and good functional groups tolerance towards excellent molecular diversity. Moreover, free 4-carboxy-isoquinolone are now for the first time generally accessible by a convergent multicomponent reaction protocol.

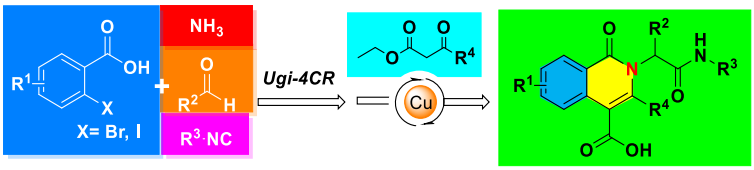

Figure 6. Isoquinolone-4-carboxylic acids by ammonia-Ugi-4CR and Cu-catalyzed cascade reaction.

In **chapter 7**, the *beta*-carbolinone scaffold is explored. This scaffold is present in natural products with diverse biological activities. The known methods usually require harsh conditions to access it. Here, we demonstrate that the main skeleton can be built by using an Ugi-four component reaction with an indole-carboxylic acid and propargyl-amine. In an one-pot fashion, without isolating the Ugi product, but by directly adding silver triflate in the reaction mixture, an intramolecular cyclization takes place and leads to the *beta*-carbolinone analogues. A library of 22 derivatives in high yields was synthesized. Docking studies of the synthesized compounds indicate that the derivatives could be useful as allosteric inhibitors of DAPK3 kinase, mimicking analogues of the natural product Bauerine C.

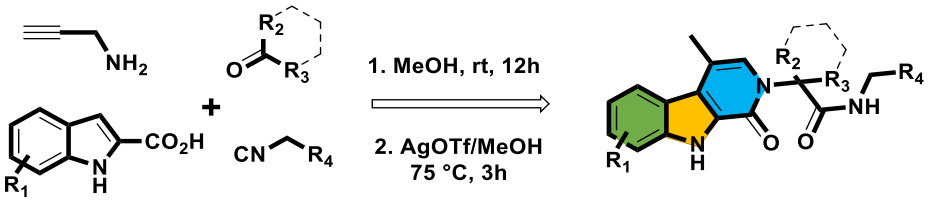

Figure 7. Ag-catalyzed facile synthesis of β-carbolinones.

In the last part of the thesis, **chapter 8**, the focus is on a very exciting new modality in medicinal chemistry, the proteolysis-targeting chimeras (PROTACs). The term was first described in 2001, but in the last few years the great potential of this approach has been clearly demonstrated. PROTACs are bifunctional molecules, targeting a protein of interest and an E3 ligase. In contrast to classical medicinal chemistry, where the aim is to inhibit a disease-related protein, PROTACs induce the degradation of the target by taking advantage of the normal proteasomal degradation process. In this relatively new field, in preclinical studies numerous targets have been successfully degraded and earlier this year the first clinical trial was announced. In chapter 8, the principles of PROTAC design were applied on the target cyclin-dependent kinases CDK4/6, which are involved in the regulation of the cell cycle and are a validated target for cancer. Since 2015, three dual kinase inhibitors have been approved by the FDA. However, achieving total selectivity has been elusive for small molecules. As shown in recent publication, selectivity could be tuned by PROTACs. Here, starting from abemaciclib, the last compound to gain FDA approval, and by applying structural modifications, abemaciclib-based PROTACs were designed and synthesized. The preliminary biological data are promising and the aim is to include *in vivo* studies for this target, which has not been performed yet by CDK4/6-PROTACs.

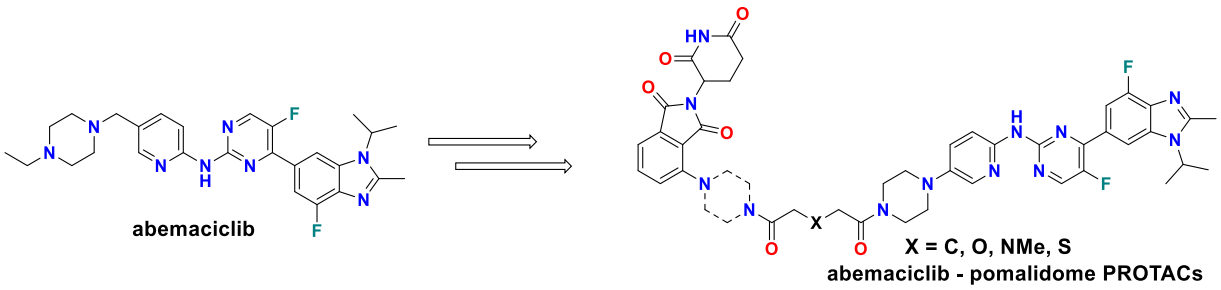

Figure 8. Structures of kinase CDK4/6 inhibitor and examples of synthesized PROTACs.

Overall, the aim of this thesis was to demonstrate that the wide-spread application of the Ugi reaction for the synthesis of a variety of heterocyclic compounds with diverse biological properties, where careful selection of the starting building blocks provided the appropriate functionality for post-Ugi modifications. So far, transition-metal-catalyzed (hetero)annulations mostly occupied the front seat in post-MCR transformation chemistry. The development of novel transformations for generating more complex drug-like structures via tuning the catalytic system, the ligands and the reactivity of the substrates as well as the investigation of the mechanistic aspects, are challenges in this field. In addition, the focus of medicinal chemistry is shifting from enzymes and proteins with well-defined pockets to protein – protein interactions and more challenging targets. The choice of the target, affects also the type of necessary chemistry and drug design. Thus, medicinal chemists are constantly developing novel methodologies and new modalities to rise to the challenges.

Contributions

In **chapter 1** I selected the topic, collected the data, defined the structure and wrote the manuscript. In **chapter 2** I synthesized all the compounds, analyzed the data and provided feedback on writing the manuscript and assisted in replying to the referees comments during the revision process. In **chapter 3** I was the project leader. I developed the methodology, performed the synthesis, analyzed the data and wrote the manuscript and performed the revision and the response to the referees. In **chapter 4** I was the project leader. I developed the methodology, performed the synthesis, supervised the project, analyzed the data and wrote the manuscript and performed the revision and the response to the referees. **In chapter 5** I was the project leader. I developed the methodology, performed the synthesis, supervised the project, analyzed the data and wrote the manuscript and performed the revision and the response to the referees. In **chapter 6** I was the project leader. I developed the methodology, performed the synthesis, supervised the project, analyzed the data and wrote the manuscript and performed the revision and the response to the referees. In **chapter 7** I synthesized part of the library, gave suggestions for troubleshooting and provided feedback on the manuscript preparation. **In chapter 8** I was involved in the synthetic part, I prepared the cereblon intermediates and performed the final coupling reactions for PROTACs. I synthesized also abemaciclib-pomalidomide PROTACs via MCR approaches.